Comments of
The Formaldehyde Panel of the American Chemistry Council
On the
Proposed Revision to the Review Process for the Report on Carcinogens[1]

November 30, 2011

Executive Summary

The National Toxicology Program (NTP) has proposed revisions to its review process for the Congressionally-mandated Report on Carcinogens (RoC) "to enhance transparency and efficiency and to enable the NTP to publish the RoC in a timelier manner." 76 Fed. Reg. 67200 (Oct. 31, 2011). In making the proposal, NTP emphasizes its intent to "maintain critical elements of the existing process, including external scientific and public involvement, scientific rigor, and external peer review." In an effort to produce the RoC in a timelier manner, however, the proposal would actually reduce transparency and would further diminish the scientific rigor of the Report. Moreover, the proposal would further insulate NTP and the RoC reviewers from scientific debate by marginalizing public involvement.

ACC's Formaldehyde Panel makes the following recommendations to restore the integrity and timeliness of the Reports while improving transparency and ensuring a vigorous scientific debate and review –

- NTP should revise the listing criteria as applied to "known" carcinogens to include the requirement for –
  - a biologically plausible mechanism,
  - an assessment of the quality of the study, or studies, on which the determination is based, and
  - a weight-of-evidence evaluation of all the available evidence.

- NTP should employ a consistent weight-of-evidence framework, formulated upon a hypothesis-based mode of action evaluation procedure, so that data from all relevant studies can be systematically reviewed, given appropriate weight, and integrated in a manner that provides a robust understanding of the mode of action.

- NTP should incorporate a standardized approach to evaluating the methods and findings of available studies, such as that recommended by the National Academy of Sciences (NAS), into the RoC process.

- NTP monographs should be subject to two separate reviews – the first by other federal agencies and the second by an independent peer review panel.

[1] 76 *Federal Register* 67200, October 31, 2011.

- Members of the independent peer review panel should be chosen through a selection process similar to that used by NAS and should represent a sufficient level and breadth of expertise to assess the particular substance to be considered.

- The listing recommendation should be made by the peer review panel after reviewing all of the available data. NTP should not develop the listing recommendation as part of the draft monograph.

- NTP should accept public comment at each stage of the review process including the selection of substances, the draft monograph, the revised draft monograph, and the final draft monograph. NTP should prepare a response to comments at each stage in the process.

I. Introduction

In 1978, Congress amended the Public Health Service Act to require the Secretary of Health, Education and Welfare, now Health and Human Services (HHS), to publish a list of known and suspected carcinogens.[2] More specifically, the Act required HHS to -

> publish an annual report which contains – a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed.[3]

The Act itself does not define or indicate the type of classification criteria that HHS should adopt or the scope of the evidence that must analyzed in classifying potential human carcinogens. The only constraints Congress placed on HHS in listing a substance in the RoC is that "there must be reasonable ground for designating a substance as a ***putative*** carcinogen."[4] (emphasis added)

The HHS Secretary delegated responsibility for preparation of the RoC to NTP which established the following criteria to be used in classifying a substance as "known to be a human carcinogen" –

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[2] *See* Biomedical Research and Research Training Amendments, Pub.L. No. 95-622, Tit. II § 262, 92 Stat. 3412, 3435-36 (1978).

[3] 42 U.S.C. § 241(b)(4) (2011).

[4] Joint House-Senate Summary, 124 Cong. Rec. 38657 (Oct. 14, 1978)

> There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

NTP has interpreted the criteria regarding carcinogenicity in humans to include consideration of all relevant information including, but not limited to, "dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance."[5]

The publication of the 12th RoC in June 2011 generated a significant amount of scientific controversy and highlighted a number of shortcomings in the process that NTP uses to generate the Report. In response, NTP has proposed a number of changes to its review process, with a primary focus on "efficiency" and "timeliness" of the production of the document. NTP's proposal, however, fails to address many fundamental problems that have been the primary cause of delays in the preparation of the RoC. These problems include –

- NTP's implementation of its mandate to designate "known" human carcinogens is inconsistent with a reasonable interpretation of the law,
- The RoC process lacks a transparent weight-of-evidence scheme for evaluating the available information,
- NTP ignores its mandate to consider exposure to substances under consideration for RoC listing,
- The current RoC process does not provide an independent peer review of available scientific information, and
- NTP's consideration of public comments is superficial and unresponsive.

Unless these issues are addressed, no amount of shuffling of the review steps will improve the quality and/or timeliness of the RoC. In light of the potentially significant risk-management implications of RoC listing, it is imperative that NTP abandon its current strength-of-evidence, precautionary approach that is neither mandated nor implied either in the Congressional mandate to NTP or in any other federal statute governing the NTP's work in this regard.

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[5] 12th Report on Carcinogens, at p. 4.

These problems are discussed below, with an explanation of how each impacted NTP's consideration of formaldehyde for the 12th RoC. Finally, these comments recommend a number of changes to the review process that would ensure the robust and objective consideration of the scientific issues, increase transparency, and allow production of the RoC on a timelier basis.

II. NTP's Implementation of its Mandate to Designate "Known" Carcinogens is Inconsistent with a Reasonable Interpretation of the Law

It is reasonable to conclude that Congress intended to limit the classification as "known" carcinogens to substances for which there exist strong evidence in human studies that is not contradicted by other equally valid evidence. This interpretation is supported by the reference to the term "putative" – suggesting that the substance is commonly regarded as a known carcinogen.[6] Yet, NTP's policy only requires that there be "sufficient" evidence from human studies without explaining what makes the evidence sufficient – except to indicate that it includes information that cannot be explained by "chance, bias, or confounding."[7] The NTP policy makes no reference, however, to the possible existence of information that contradicts the information on which NTP chooses to depend. NTP's policy provides no objective criteria for how it will consider the weight of evidence available.

The current policy allows NTP to list a substance as a "known" carcinogen solely if it can find human data that is not due to chance – even if that human data is contradicted by other equally valid data, if no biologically plausible causal basis for an association can be established, and/or if the substance is <u>not</u> generally regarded as a carcinogen by the scientific community. NTP's proposed revisions to the RoC review process do not address the failure to meet its statutory mandate to develop a reasonable basis for identifying "known" carcinogens.

- <u>Impact on NTP's Consideration of Formaldehyde</u>

The 12th RoC indicates that there is sufficient evidence of cancer for formaldehyde from studies in humans for nasopharyngeal (NPC), sinonasal, and lymphohematopoietic (LHP) cancer, specifically myeloid leukemia. In the course of its deliberations, NTP received extensive comments on the epidemiological evidence for formaldehyde. These data also were

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[6] It can be further argued that Congress intended that NTP only consider the carcinogenic potential of a substance at typical levels of exposure.

[7] This interpretation is derived from the NTP's discussion of the human evidence for a substance designated as "reasonably anticipated to be a human carcinogen." In defining "reasonably anticipated," NTP reasons that there is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded."

considered by an expert panel convened by the National Academy of Sciences (NAS)[8] and by the International Agency for Research on Cancer (IARC).[9] The IARC panel concluded that there was only limited evidence for sinonasal cancer. The NAS panel reported a number of important limitations in the available epidemiologic data for LHP cancer and leukemia including "uncertainties of exposure assessment, possible confounding by other pollutants, and reliance on mortality rather than incidence data."[10]

Regarding the epidemiological evidence on formaldehyde exposure and NPC, a detailed analysis submitted to NTP reported little support for causation, with most studies not demonstrating an increased risk.[11] The only positive association was noted in Hauptmann et al. (2004),[12] which was limited to an excess of NPC from one study plant. As noted by the NAS expert panel, this raises concerns about the "generalizability of the findings to the other facilities and to other workers exposed to formaldehyde" as well as the "possibility that the results were confounded by other pollutants present at that one facility."[13]

NTP's conclusions regarding LHP cancer are based on data from a cohort study by the National Cancer Institute (NCI), [14] an NCI study among embalmers, [15] and a meta-analysis by Zhang *et al.* (2009). [16] The most recent update of the NCI formaldehyde workers cohort does not demonstrate excesses of leukemia or myeloid leukemia deaths, even after the omission of 995 (incorrectly reported as 1,006) deaths is considered. Except for use of the "ever peak" as the dose metric, various quantitative exposure metrics produced no clear or statistically significant associations, including more appropriate "cumulative" or "cumulative peak"

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8 NAS. 2011. Review of the Environmental Protection Agency's draft IRIS assessment of formaldehyde. Committee to Review EPA's Draft IRIS Assessment of Formaldehyde. Board of Environmental Studies and Toxicology. Division of Earth and Life Sciences. Available at http://www.nap.edu/catalog.php?record_id=13142

9 Baan, R et al. 2009. A review of human carcinogens—Part F: Chemical agents and related occupations. Lancet Oncol. 10(12): 1143-1144.

10 NAS (2011), at p. 83.

11 Environ Corp (2011). National Research Council report on scientific evidence pertaining to the relationship between formaldehyde exposure and leukemia: Implications for the National Toxicology Program's listing of formaldehyde in the 12th Report on Carcinogens. Prepared on behalf of the American Chemistry Council (April 22, 2011).

12 Hauptmann et al., 2004. Mortality from solid cancers among workers in formaldehyde industries. American Journal of Epidemiology 159(12):117-1130.

13 NAS. 2011. at p. 64. In light of these concerns, the expert panel encouraged EPA to update its NPC assessment once NCI completes its follow up of the cohort to 2004.

14 Beane Freeman et al., 2009. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute cohort. Journal of the National Cancer Institute 101(10):751-761.

15 Hauptmann et al., 2009. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. JNCI 101:1696-1708.

16 Zhang et al., 2009. Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms. Mutation Research 681(2-3):150-168.

exposure metrics. A review of the NCI embalmer study by Cole (2010) [17] suggests a number of significant limitations, including several potential indicators of selection bias. Importantly, the study does not demonstrate an excess of myeloid leukemia deaths. The findings of the meta-analysis by Zhang *et al.* (2009) are inconsistent with the more recent work by Bachand *et al.* (2010)[18] and by Schwilk *et al.* (2010)[19] - neither of these was used in NTP's analysis. After a review of the primary literature and the 2010 meta-analyses of the epidemiology data, NAS noted that -

> The committee recommends caution . . . in using meta-analyses performed by others to assess causality or to quantify effects. Meta-analysis can be a valuable method for summarizing evidence but can also be subject to variable interpretations depending on how literature is selected and reviewed and data analyzed.[20]

III. The RoC Process Lacks a Transparent Weight of Evidence Scheme for Evaluating the Available Information

Aside from the definition outlined above, NTP provides no objective criteria for how it will consider scientific information in determining whether a substance is a "known" carcinogen. NTP fails to provide any indication for what type and/or amount of human evidence are "sufficient" to designate a substance as a "known" carcinogen.[21] Although NTP indicates that it will also consider "dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance," moreover, it provides no indication of how that information is to be incorporated into its determination. As such, there is no basis for objectively assessing whether NTP has met its threshold for determining that a substance is a "known" carcinogen. NTP appears to reserve complete discretion in selecting the data available for a substance to be considered and the evaluation of that data. Such unbridled discretion in designating a substance as a "known" carcinogen, in light of the potential impacts of RoC listing, is inappropriate. The proposed revisions do not

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[17] Cole et al., 2010. Formaldehyde and lymphohematopoietic cancers: A review of two recent studies. Regulatory Toxicology and Pharmacology. 58:161-166.

[18] Bachand et al., 2010. Epidemiological studies of formaldehyde exposure and risk of leukemia and nasopharyngeal cancer: A meta-analysis. Critical Reviews in Toxicology 40(2):85-100.

[19] Schwilk et al., 2010. Formaldehyde and Leukemia: An updated meta-analysis and evaluation of bias. Journal of Env Medicine. 52(9):878-886.

[20] NAS. 2011, at pp. 83-84.

[21] IARC considers *sufficient evidence of carcinogenicity* to mean that "a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence." Although NTP appears to define "sufficient evidence" similarly, it does not require that a causal relationship be established.

offer a weight of evidence approach for assessing the available scientific information that is objective and transparent.

- Impact on NTP's Consideration of Formaldehyde

The conclusions of the 12th RoC differ from those reached by expert panels recently convened by NAS and IARC to review the potential risks of formaldehyde. These differences suggest that there is a considerable amount of controversy surrounding the interpretation of the available evidence for formaldehyde. NTP has provided two separate explanations of its basis for listing – the substance profile in the 12th RoC and a subsequent Addendum that specifically addresses the findings of the NAS expert panel. Both documents summarily dismiss those data that do not support its determination while ignoring the shortcomings of data that support its conclusions. In discussing the report of the NAS expert panel, for example, the Addendum dismisses the NAS panel's report saying that it is of "limited applicability" to the NTP RoC evaluation, while embracing those aspects of the NAS report that are consistent with NTP's own. The Addendum indicates, moreover, that mechanistic data provide "supporting evidence" for its determination while concluding that an understanding of the mode of action is not required for RoC listing when the data do not support its conclusions.

While NTP may have correctly interpreted those data it selected for inclusion in the analysis, the failure to consider all of the available data is a significant shortcoming of its assessment for formaldehyde. While the Addendum suggests that the NAS review "is not an independent hazard assessment," it is, in fact, the RoC that falls short as an independent and comprehensive assessment.

IV. NTP Ignores its Mandate to Consider Exposure to Substances under Consideration for RoC Listing

The Public Health Service Act, as amended, requires that NTP include in the RoC those substances to which "a significant number of persons residing in the United States are exposed." The Act further specifies that the RoC include "information concerning the nature of such exposures and the estimated number of persons exposed to such substances." Thus, while Congress does intend that NTP conduct an assessment of hazard and exposure as part of the RoC analysis, it does specify that NTP put the cancer hazard presented by a substance in the context of typical exposures.

Although the dose at which a carcinogenic effect is observed in humans or animals is critically important to the practical utility of RoC listing for decision-making, exposure has no bearing on NTP's decisions. The disclaimer that a RoC listing "only indicates a potential hazard

and does not establish the exposure conditions that would pose cancer risks,"[22] is incompatible with NTP's Congressional mandate – particularly considering the incomplete nature of its hazard assessment. NTP's proposed revisions to the RoC review process do not address the failure to address exposures.

- Impact on NTP's Consideration of Formaldehyde

The issue of exposure is of critical importance in considering potential risks presented by formaldehyde, especially in light of the fact that formaldehyde is an essential metabolic intermediate and is formed naturally in the human body and in most living organisms. Yet the RoC includes only a token discussion of endogenous production and its significance to assessing potential risks associated with exposure to other sources of formaldehyde. Although reference is made to endogenous concentrations of 2 to 3 micrograms/gram in blood of humans, monkeys, and rats, NTP fails to place these values in the context of other potential exposures.

V. The Current RoC Process Does Not Provide an Independent Peer Review of Available Scientific Information

Although NTP repeatedly points to the "peer review" of its RoC decisions, the review process does not involve a truly independent and well-qualified group of experts to review both the body of science for a particular substance, and the listing decision for that substance.

As indicated above, there is no way to assess to what extent information that does not support listing in the RoC is considered in NTP's evaluation. Based on the available information, it would appear that negative and equivocal evidence play a minor and highly subordinate role. This perception is supported an exchange between a member of the Board of Scientific Counselors (BSC) and NTP staff during the June 21, 2010, meeting to consider glass wool fibers:

> [BSC member] Dr. [Mitzi] Nagarkatti asked whether animal studies had been conducted in species other than rats and hamsters, and if so, why they were not included. [NTP staff member] Dr. [Gloria] Jahnke replied that there had been studies in guinea pigs, as well as inhalation studies in monkeys, that had been negative. She explained that she did not include negative results in her presentation, ***as it is the practice to only report studies that support the listing recommendation***.[23] [emphasis added]

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[22] 12th RoC, at p. 3.

[23] BSC. Summary minutes of NTP Board of Scientific Counselors meeting, June 21-22, 2010, at p. 16. Available at http://ntp.niehs.nih.gov/ntp/about_NTP/BSC/2010/June/minutes20100622.pdf.

NTP Director Linda Birnbaum reiterated NTP's practice to exclude information that does not support listing in a subsequent discussion of formaldehyde at the same meeting:

> Dr. [Linda] Birnbaum reminded attendees that the RoC is mandated to list known or suspected carcinogens and as such is not a risk assessment document, as the EPA's IRIS documents are. ***She reiterated that the substance profile is designed to provide evidence in support of the conclusions that have been reached, and not to include all of the negative information as well***.[24] [emphasis added]

The NTP's listing criteria, therefore, provide no transparent way a presumption of human carcinogenicity might be rebutted either by the peer reviewers or the general public. This lack of transparency is made even more apparent when considering NTP's charge to the BSC as part of their review for the 12th RoC to "determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated, and supports the NTP's preliminary policy decision regarding its listing in the RoC."[25] Clearly if the reviewers are provided with little or no information that does not support NTP's decision, it is highly unlikely that they could or would challenge NTP's recommendations.

Even if the BSC members wanted to provide comment on the listing decision, however, the current RoC process excludes the BSC "peer reviewers" from doing so as the RoC listing is a "policy" rather than a "scientific" decision. It is ironic that the august body appointed to provide scientific counsel to NTP is the only group who is not able to comment on a listing recommendation.

The concern is equally valid for the expert panels, who are asked to review the NTP's draft background document without the full benefit of public comment to the draft and NTP's response to these comments. Based on the draft, the experts are asked to "identify any missing information from the body of knowledge presented in the document, and determine the utility of the body of knowledge in the background document for drawing conclusions about the carcinogenicity of a candidate substance."[26] Notwithstanding their scientific expertise, panel experts could not be expected to "identify any missing information" without the benefit of robust public input or an objective document discussing both positive and negative studies for the chemical under review. Following its review of the draft, the expert panel is then asked "to apply the criteria for listing in the RoC to the available body of knowledge and make a recommendation regarding listing status for the candidate substance."

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[24] Id., at p. 43.

[25] Id., at p. 12. Minutes are not available for the meetings for the expert panel convened to consider the substance profiles for the 12th RoC.

[26] NTP explanation of the charge to the expert panels for the 12th ROC. (Available at http://ntp.niehs.nih.gov/?objectid=DFAFC5A1-F1F6-975E-766CD2956416305E.)

Based on the ill-defined, non-scientific criteria presently laid out in NTP's policy, the expert panel is being asked to make a purely policy decision. These concerns are further heightened by NTP's failure to ensure that the expert panel possesses a sufficiently broad level of expertise in the substance and health end points to be considered.

The proposed revisions do not allow for independent peer review of available scientific information. The proposal would reduce the number of expert panel reviews from two to one, and give NTP the discretion to choose whether the review is performed by the BSC (subject to FACA requirements) or by an ad hoc panel. NTP would retain sole discretion in selecting candidate substances and would now also be in charge of developing the listing recommendation. In addition, the BSC or ad hoc panel would continue to be limited in its ability to reject NTP's listing recommendation.

- Impact on NTP's Consideration of Formaldehyde

NTP's consideration of the available information for formaldehyde is highly selective in both the studies chosen for inclusion and the findings from those studies that are referenced. While not an exhaustive list, examples of the shortcomings of the NTP assessment include –

- NTP ignores the explicit findings to the contrary of the authors of the NCI study on which it relies to support its findings regarding formaldehyde and leukemia. In their paper, the authors note "there was no evidence that risks increased with cumulative number of peaks $\geq$ 4.0 ppm [parts per million] or for duration of exposure ***for any cause of death evaluated*** (data not shown)."[27] (emphasis added)

- NTP fails to fully consider multiple shortcomings of the meta-analysis by Zhang et al. (2009) on which it depends.

- In contrast, NTP wholly dismisses the meta-analysis by Bachand et al. (2010) that does not support its determination, despite the fact that it is the only analysis to use standard analytical methods and the only one to include data from nearly 1000 missing deaths not reported in earlier publications.

- NTP ignores recent publications by Lu et al. (2010)[28] and others that refute its assertion that formaldehyde is systematically distributed in humans. The failure

[27] Beane Freeman et al., 2009, Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute cohort. Journal of the National Cancer Institute 101(10):751-761. at 755.

[28] Lu et al., 2010. Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. Toxicol Sci. 116:441-451.

to observe systematic delivery is critical to assessing whether the allegation that formaldehyde causes leukemia is biologically plausible.[29]

- NTP relies on the 2000 version of the World Health Organization's indoor air guideline for formaldehyde, rather than the 2010 guidelines[30]

- Despite NTP's emphasis on human data, the expert panel convened for formaldehyde lacked sufficient epidemiology expertise and included no one with any expertise on leukemia and other LHP cancers.

In spite of the selective nature of NTP's presentation to the BSC during its review of the substance profile for formaldehyde, several members voiced their strong misgivings about the listing of formaldehyde as a "known" carcinogen with respect to leukemia. While such misgivings should have prompted further consideration of the recommendation, NTP staff already had cautioned the members that it was not within the BSC's charge or authority to address the NTP's listing decision concerning formaldehyde.

Throughout the RoC review process, NTP blurred the distinction between the evidence of association between NPC, sinonasal cancer and leukemia and formaldehyde such that the ultimate listing of formaldehyde as a "known" human carcinogen was condensed into a few, simple statements that included all three endpoints in the listing decision. NTP continued to blur the distinction despite specific entreaties from several industry-sponsored scientists that the practice ran afoul of basic principles of sound scientific assessment.

VI. NTP's Consideration of Public Comments is Superficial and Unresponsive

In response to concerns expressed about the RoC review process and to address guidance from the Office of Management and Budget (OMB),[31] NTP made a number of changes to the RoC review process in 2007. The most significant of these changes were the (1) addition of an expert panel to review NTP's draft background document and (2) a public peer review of the draft substance profiles by the BSC. NTP also agreed to allow public comment on the substances proposed for listing and on the draft background document and to prepare a response to public comments on a trial basis for the 12th RoC. Fortunately, NTP dropped its proposal to conduct the BSC peer review in closed session.

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[29] The RoC Addendum acknowledges this lack of biological plausibility, but concludes that "[a]ppreciation of 'mode of action,' or an understanding of how exposure to a given substance might lead to cancer, is an important piece of supporting evidence, but is not a requirement for listing in the RoC."

[30] WHO. 2010. WHO Guidelines for Indoor Air Quality. Chapter 3 Formaldehyde. Available at http://www.euro.who.int/en/what-we-publish/abstracts/who-guidelines-for-indoor-air-quality-selected-pollutants.

[31] OMB. Final information quality bulletin for peer review. (December 15, 2004).

Although the 2007 notice provided additional opportunity for public comment, NTP did not explain how it planned to consider these comments or what obligation it has for providing public comments to the peer review panels. Clearly, if NTP documents are intended to "provide evidence in support of the conclusions that have been reached, and not to include all of the negative information as well," as indicated by Dr. Birnbaum, it is unlikely that comments from the public that oppose RoC listing will be incorporated. In the only instance where NTP's responses to public comment have been made available, the responses were largely a recitation of previously stated positions without any effort to address the issues being raised by the commenter. In several cases, NTP chose either to mischaracterize the nature of those comments or did not address significant aspects of the comments received.

Despite NTP's suggestions to the contrary, the proposed revisions reduce public participation and further obscure the transparency of the process. As proposed, the process revisions would reduce the opportunities for public comment from four to three and eliminate the short-lived requirement for NTP to respond to comments received from the public. Comments received during the interagency review process would continue to be kept confidential.

- Impact on NTP's Consideration of Formaldehyde

The conclusions reached by NTP in support of its designation of formaldehyde as a "known" carcinogen stand in stark contrast to the public comments received. This contrast can be seen most clearly in NTP's consideration of the evidence for leukemia where commenters considering the same body of scientific data as NTP reached the exact opposite conclusion as to the sufficiency of the human data. Rather than address the inconsistencies between the NTP and NAS analyses pointed out by commenters, the NTP Addendum dismisses them as of "limited applicability" while fully embracing the consistencies.

VII. Proposed Revisions to the RoC Process

Far from improving the transparency and scientific integrity of the RoC process, NTP's proposed revisions perpetuate its shortcomings while further insulating NTP from scrutiny and the obligation to provide an objective analysis of the evidence for RoC listing. The proposal would ensure that NTP has sole discretion in determining which substances are to be considered for listing, when those substances will be listed, how a substance should be listed, what body of evidence meets the listing criteria, and who should review NTP's listing decision. If implemented, the proposal would ensure that controversy continues to surround the RoC and virtually guarantees both poor quality documents and longer delays in its publication.

Faced with this likely outcome, the FA Panel offers an alternative approach to revising the RoC review process that can restore the integrity and timeliness of the documents while

improving transparency and ensuring a vigorous scientific debate and review. This approach would –

- clarify NTP's policy pertaining to the criteria for listing as a "known" and "reasonably anticipated" carcinogen,
- renew the focus on scientific decision-making, rather than on policy determinations, and
- create an open and objective review process that encourages, rather than dismisses, scientific controversies and differences in interpretations of the available information.

Listing Criteria

As described elsewhere, the criteria for listing substances in the RoC include the subjective terms "sufficient" and "limited" regarding the available human evidence which NTP has interpreted in a manner that is inconsistent with an evidence-driven evaluation. Listing as a "known" carcinogen requires only that there be human evidence that cannot be explained by "chance, bias, or confounding." If such evidence exists, NTP presumes that it indicates a causal relationship regardless of whether a causal basis can be established or even if an association is biologically plausible. NTP's analysis of the available epidemiology also is quite subjective in focusing on those studies that support causality while largely ignoring studies that do not. The information that the expert panel and the BSC are asked to review, therefore, is not sufficiently comprehensive to allow the reviewers to make an informed judgment on the validity of NTP's work.

The FA Panel recommends that the listing criteria as applied to "known" carcinogens be revised to include the requirement for –

- a biologically plausible mechanism,
- an assessment of the quality of the study, or studies, on which the determination is based, and
- a weight-of-evidence evaluation of all the available evidence.

These criteria should be made available for public review and comment and, once finalized, applied consistently in all RoC evaluations.

Focus on Scientific Decision-Making

In light of the challenges in interpreting NTP's existing listing criteria, it has been difficult to understand what standards the Agency applies in considering data as it develops its background documents and draft profiles. Unfortunately, NTP has used the listing criteria to

restrict the data to be considered and evaluated, suggesting that only data that support a listing determination are given any weight in the evaluation. Reviewers have been provided with information developed by NTP that does not provide the full context for evaluating a substance, without the benefit of the public discourse about this information, and have been asked to render judgment on its adequacy. By NTP's own admission, the listing decision is a policy determination, rather than a scientific decision.

The FA Panel recommends that NTP employ a consistent weight of evidence framework, formulated upon a hypothesis-based mode of action evaluation procedure, so that data from all relevant studies can be systematically reviewed, given appropriate weight, and integrated in a manner that provides a robust understanding of the mode of action. Such a framework is described in Chapter 7 of the NAS expert panel's report on the draft formaldehyde IRIS assessment. The FA Panel further encourages NTP to incorporate a standardized approach to evaluating the methods and findings of available studies, such as that recommended by the NAS panel, into the RoC process. In evaluating observational epidemiological studies, for example, the NAS report recommends that following items be considered –

- approach used to identify the study population and the potential for selection bias
- study population characteristics and the generalizability of findings to other populations
- approach used for exposure assessment and the potential for information bias, whether differential (nonrandom) or nondifferential (random)
- approach used for outcome identification and any potential bias
- appropriateness of analytic methods used
- potential for confounding to have influenced the findings
- precision of estimates of effect
- availability of an exposure metric that is used to model the severity of adverse response associated with a gradient of exposures. [32]

NTP's proposal for implementing such a standardized approach to evaluating data for the RoC should be made available for public review and comment. Once finalized, the approach should be applied consistently in RoC listing evaluations to provide the public and peer reviewers with a clear and comprehensive understanding of what data exist and how NTP interpreted that data. In this way, reviewers will be able to more clearly assess scientific controversies and the evidence for and against a listing determination.

<u>Open and Objective Review Process</u>

As described in more detail elsewhere, the review process employed for the 12th RoC was not conducive to an open scientific dialogue between NTP, the review panels, and the

[32] NAS, at p. 118.

public. The process, in fact, insulated the reviewers from such a dialogue. Although the public had several opportunities to provide comment, that input was not incorporated into NTP's evaluation or provided to the review panels in a manner in which it could be properly assessed. NTP's proposed changes would further insulate NTP and reviewers from a public discourse about the science. It would deprive the reviewers of the opportunity to consider opposing data and viewpoints that would better inform their ultimate decision.

The FA Panel recommends that NTP monographs be subject to two separate reviews – the first by other federal agencies and the second by an independent peer review panel. The peer review panel members should be chosen through a selection process similar to that used by the National Academy of Sciences and should represent a sufficient level and breadth of expertise to assess the particular substance to be considered.

The FA Panel strongly opposes the proposal that NTP develop a listing recommendation as part of the draft monograph. Such an approach would continue to blur the lines between science and policy considerations. The FA Panel recommends that, after having reviewed the available data, the independent peer review panel should develop the listing recommendation.

To ensure transparency and a full discussion of the science, the FA Panel recommends that NTP receive public comment at each stage of the review process – including the selection of substances, the draft monograph, the revised draft monograph, and the final draft monograph (with listing recommendation). The comments received, including comments from the interagency review, should be made available to the public. NTP should prepare a response to comments at each stage in the process in order to ensure that subsequent reviews benefit from the information that has been provided.